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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/003,669	11/01/2001	Robert H. Broyles	OKL010-107/00727A	5327

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	10/003,669	BROYLES ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 17 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires *4* months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☒ A Notice of Appeal was filed on *17 May 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☒ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: _____.

Claim(s) rejected: *1,19,22,24,25 and 27*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

JANICE LI
PATENT EXAMINER

Continuation of 3. Applicant's reply has overcome the following rejection(s): the first paragraph of 35 U.S.C. 112 with regard to written description requirement.

Continuation of 5. does NOT place the application in condition for allowance because:
As an initial matter, it is noted that the amendment and response are not fully responsive to the last Office action because applicants fail to address the requirement for sequence compliance.

Claims 1, 19, 22, 24, 25, and 27 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The arguments would be addressed in the order they presented in the Remarks.

A. Applicants first asserted that the examiner has dismissed out of hand the evidence of record regarding the expression of ferritin-H using genetic transformation.
In response, the Office has acknowledged repeatedly the in vitro findings based on nucleic acid transformation experiments disclosed both in the prior art of record (e.g. Picard et al) and in the instant specification (e.g. page 9, paper #16). It is based on the art-known hurdles for in vivo protein delivery and the clinical reality in the therapy of sickle cell disease, that the claimed therapeutic method is questioned for support of enablement.
The arguments regarding additional data newly provided are moot since these data have not been considered for the reason indicated in box 6.

B. With respect to claim 25, although the matter of cell-protein contacting is not an issue, the nucleus delivery of the ferritin-H is at issue. Further, assuming the ferritin-H could be properly delivered to the nucleus of a target cell, and the transcriptional activity of b-globin promoter could be repressed, since the half-life of a protein is short, the specification fails to teach upon cell transplantation, whether the repression could last long enough so that the disease phenotype could be corrected by the cell implant. It is the questions of kind that the office concluded that the specification fails to provide an enabling disclosure for claim 25.
Applicants then cite In re Brana and allege that the examiner is posing an incorrect question improperly require clinical effective data for supporting enablement of the claimed invention. In response, it is noted that In re Brana case law discusses whether a claimed compound has the asserted utility to be used in vivo, not a method claiming treatment effect in humans. It is also noted that the Office did not require a clinical trial to support the claimed method, but question the correlations of in vitro nucleic acid transformation data with respect to the scope of the claims drawn to in vivo protein therapy, and question whether the claimed method is fully enabled based on the teachings of those skilled in the art such as Mankad and Broyles. This is appropriate because 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970).
Applicants then cite In re Marzocchi and accuse that the examiner offered no explanation as to why those of skill in the art would not expect to achieve a clinical benefit. In response, the explanations have been offered in pages 9 through 13 of paper #16, and pages 4-7 of the Office action mailed 1/14/04, reviewing the state of art concerning therapy for sickle cell disease before and after the instant filing date and compared such to the guidance provided in the specification, raising issues such as art known hurdles in protein therapy and protein nucleus delivery as taught by the skilled artisan, e.g. Buckel et al, and pointing to the distance between basic molecular research and clinical therapy such as taught by Mankad et al. Applicants are reminded that In re Marzocchi also teaches "In the field of chemistry generally, there may be times when well-known unpredictability of chemical reactions will alone be enough to create reasonable doubt as to accuracy to broad statement put forward as enabling support for claim; this will especially be the case where statement is, on its face, contrary to generally accepted scientific principles, etc".

The arguments in Points C & D of the remarks are moot because they relied on the newly submitted declaration and exhibits, which have not been considered for the reason indicated in box 6..